REMARKS

Reconsideration of this application is respectfully requested.

Claims 238-272, 274-297, 299-308 and 310-338 were previously pending in this application. Claims 238, 272 and 308 have been amended above. No other claims have been amended, added or canceled by this paper. Accordingly, claims 238-272, 274-297, 299-308 and 310-338 as amended are presented for further examination on the merits.

Acknowledgement is made regarding the change of art unit designated for this application. Any and all future correspondence will be directed to Group Art Unit 1631 which is now believed to be designated for this case.

Applicants appreciate that the finality of the previous office action has been withdrawn and that their previous submission after final filed on November 20, 1998 has been entered. Applicants also appreciate the indication on page 2 in the September 28, 1999 Office Action that rejections and/or objections not reiterated from previous office actions have been withdrawn.

In response to the Examiner's remarks, a new section titled "Brief Description of the Drawings" has been inserted into the specification above.

In a sincere effort to define their claimed invention more clearly and to place it in an allowable condition, Applicants have amended claims 238, 272 and 308 above. As amended above, the preamble of claim 238 recites "[a]n oligo- or polynucleotide capable of hybridizing with or binding to a nucleic acid sequence of interest, said oligo- or polynucleotide comprising at least one chemically modified nucleotide having the formula:

Sig
||
PM – SM – BASE.

Claim 238 further recites "wherein PM is a phosphate moiety, SM is a sugar moiety comprising a pentose sugar selected from the group consisting of a ribose, a deoxyribose and a dideoxyribose, and BASE is a pyrimidine, purine or 7-deazapurine moiety, said PM being covalently attached to a position of SM selected from the group consisting of the C2', the C3' and the C5' position, said BASE being covalently attached

to the 1' position of SM from the N^1 position when BASE is a pyrimidine or the N^9 position when BASE is a purine or 7-deazapurine, and said Sig is covalently attached to a position of SM selected from the group consisting of the C2', the C3' and the C5' position directly or through a linkage group and Sig is a moiety which is detectable when said nucleotide is incorporated into a double-stranded nucleic acid duplex or complex." In the latter recitation, therefore, Markush language has been inserted in three instances, first, with regard to the members of SM (dideoxyribose having been added), second, with respect to the covalent attachment of PM to SM, and third, with regard to the covalent attachment of Sig to SM. Finally, the term "or complex" has been inserted at the end of claim 238. Similar amendments have also been made in claim 308. Claim 272 which has been allowed has also been amended to recite "[a] chemically modified nucleotide."

It is believed that the above amendments to the claims serve to clarify Applicants' present invention and to substantially narrow the issues in this application, thereby expediting prosecution. None of these amendments are believed to involve the insertion of new matter into the original disclosure. Instead, these amendments are believed to comprise subject matter that Applicants are duly entitled to claim.

The Requirement Under 37 C.F.R. §1.74

In the Office Action (page 2), the Examiner noted that "[t]he specification lacks a section directed to "Brief Description of the Drawings" as required in 37 CFR § 1.74." As indicated above, Applicants have inserted such a section in accordance with the Examiner's requirements.

The Rejection Under 35 U.S.C. §102(b)

Claims 238, 240-243, 245, 246, 249, 255, 256, 262, 264, 265, 267-271, 306, 308, 310-313, 315, 316, 319, 325, 326, 329-333, and 336-338 stand rejected under 35 U.S.C. §102(b) as being anticipated by Kourilsky et al.(GB 2,019,408). In the Office Action (page 3), the Examiner stated:

> Kourilsky et al. discloses the preparation of nucleotide, deoxynucleotides, and oligomers thereof with biotin labels as well as mercury and SH groups on page 2, lines 34-52. The polynucleotides

attached to a particular nucleotide via the sugar-phosphodiester backbone meets the requirements of the instantly claimed and linked Sig moieties attached to a nucleotide with a phosphate moiety also attached.

The anticipation rejection is respectfully traversed.

As indicated in the opening remarks above, claims 238, 272 and 308, each being independent, have been amended. The preambles to claims 238 and 308 recite that the oligo- or polynucleotide (claim 238) or the composition comprising a polymeric compound (claim 308) are "capable of hybridizing with or binding to a nucleic acid sequence of interest." Claim 272 also defines in its preamble "[a] chemically modified nucleotide." Moreover, both claims 238 and 308 recite that such oligo- or polynucleotide or composition comprises or has attached at least one chemically modified nucleotide.

In order to sustain an anticipation rejection, there must be an identity of material elements between the claimed invention and the cited document. In the case of Applicants' presently claimed invention, there are at least two material elements lacking in the cited Kourilsky document. In the portion cited by the Examiner, Kourilsky et al. discloses two methods for chemical modification of their probe. The first method is the so-called Manning technique disclosed in two publications [Manning et al., "A New Method of *in situ* Hybridization," Chromosoma (Berl.) 53:107-117 (1975); and Manning et al., "A Method for Gene Enrichment Based on the Avidin-Biotin Interaction. Application to the *Drosophila* Ribosomal RNA Gene," Biochemistry 16:1364-1370 (1977)]. The Manning technique is limited to RNA and involves the oxidation of the sugar at the 2' and 3' positions, in effect, breaking open the ring and destroying the structural integrity of the nucleotide that is no longer a nucleotide. This highly disruptive and ring-destroying technique was later used by Dr. Norman Davidson's group, including Broker et al. ["Electron microscopic visualization of tRNA genes with ferritin-avidin:biotin labels," Nucleic Acids Research 5:363-384 (1978)] and Angerer et al. ["An Electron Microscope Study of the Relative Positions of the 4S and Ribosomal RNA Genes in HeLa Cell Mitochondrial DNA," Cell 9:81-90 (1978)].

In the case of Applicants' invention, the claims define a chemically modified nucleotide or an oligo- or polynucleotide or composition comprising or having a chemically modified nucleotide attached thereto. The Manning technique disclosed in the cited Kourilsky document does not entail a chemically modified nucleotide, any such nucleotide having been destroyed in Manning's highly disruptive modification method.

Kourilsky et al. also refer to a second method for probe modification, the so-called Avrameas method [Stratis Avrameas, "Coupling of Enzymes to Proteins with Glutaraldehyde. Use of the Conjugates for the Detection of Antigens and Antibodies," Immunochemistry 6:43-52 (1969)]. The Avrameas method is an old technique found to be very unreliable in making nucleic acid probes. It discloses the use of glutaraldehyde, which when combined with nucleic acid, produces substantial crosslinking involving the amino groups of any cytosine, adenine and guanine bases. The nucleic acid so modified by the Avrameas method is a poor probe for hybridization and detection for at least two reasons. First, the bonding otherwise provided by amino groups in the bases is stymied. Second, the crosslinked nucleic acid will bind to other probes nonspecifically, again, making for poor target hybridization and detection.

As indicated above, Applicants' claimed invention is capable of hybridizing with or binding to a nucleic acid sequence *of interest*, unlike any probe disclosed by Kourilsky et al. that was modified by the Avrameas method.

In view of the above amendments to the claims and the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the anticipation rejection.

Applicants sincerely appreciate the indication that claims 272, 274-297, 299-305 and 307 are allowed. Furthermore, they acknowledge, again with appreciation, that claims 244, 247-248, 250-254, 257-261, 263, 266, 314, 317-318, 320-324, 327-328 and 334-335 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. In view of the above amendments to the independent claims in this application, it is believed that the foregoing claims do not need to be rewritten as such at this time.

Supplemental Information Disclosure Statement

In accordance with their duty of disclosure under 37 C.F.R. 1.56, and pursuant to the provision of 37 CFR 1.97-1.98, Applicants, through their attorney, are bringing twenty (20) documents to the attention of the Examiner and the United States Patent and Trademark Office. These documents, including Manning's 1977 Biochemistry and Avrameas' 1969 Immunochemistry publications, discussed *supra*, are included in the

Supplemental Information Disclosure Statement being concurrently filed with this Amendment.

Early and favorable action is respectfully requested.

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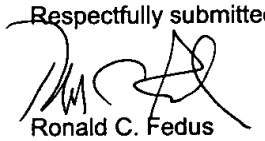
SUMMARY AND CONCLUSIONS

Claims 238-272, 274-297, 299-308 and 310-338 are presented for further examination. No claims have been added or canceled by this Amendment.

This Amendment is accompanied by a Request For An Extension Of Time (3 months) a Notice of Appeal, and authorization for the large entity fees therefor. No other fees are believed due in connection with this filing. In the event that any other fee or fees are due, however, the Patent and Trademark Office is authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, and to credit any overpayment thereto.

In view of the above discussion of the issues and amendments to the claims, Applicant respectfully submits that all of the instant claims are in allowable condition. Should it be deemed helpful or necessary, the Examiner is respectfully invited to telephone the undersigned at (212) 583-0100 to discuss the subject application.

Respectfully submitted,



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